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(54) CRYSTALLINE 4-AMINO-2-(2,6-DIOXOPIPERIDINE-3-YL) ISOINDOLINE-1,3-DIONE MONOHYDRATE, COMPOSITIONS AND METHODS OF USE THEREOF

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(58) **Field of Classification Search**

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(57) **ABSTRACT**

Provided herein is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate. Pharmaceutical compositions comprising the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate are also disclosed.

9 Claims, 4 Drawing Sheets

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Celgene Corporation Awarded Additional Patent Protection for Lead IMiD(TM), Revimid(TM); Comprehensive Patent Protection

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FIG. 1

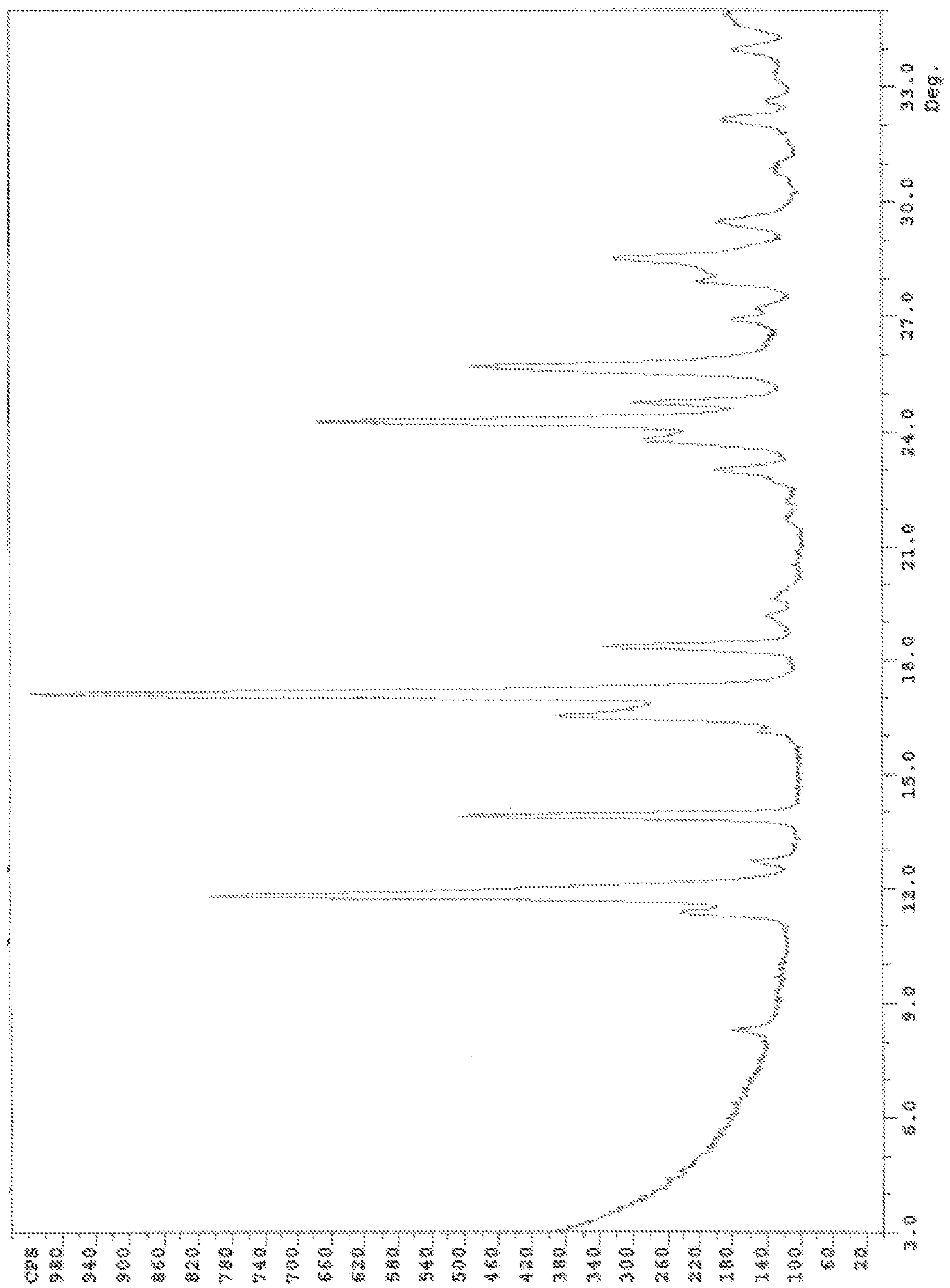
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FIG. 2

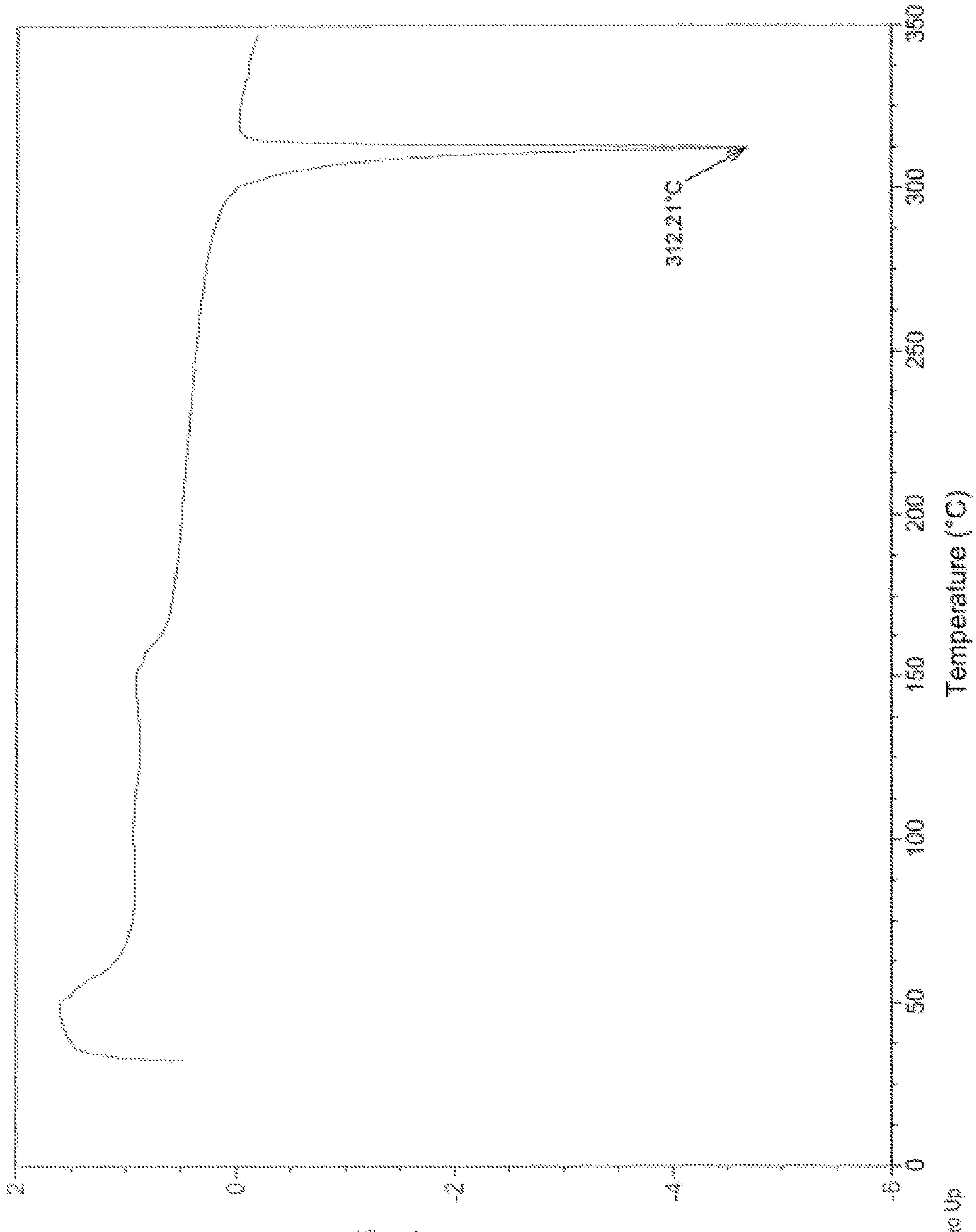
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FIG. 3

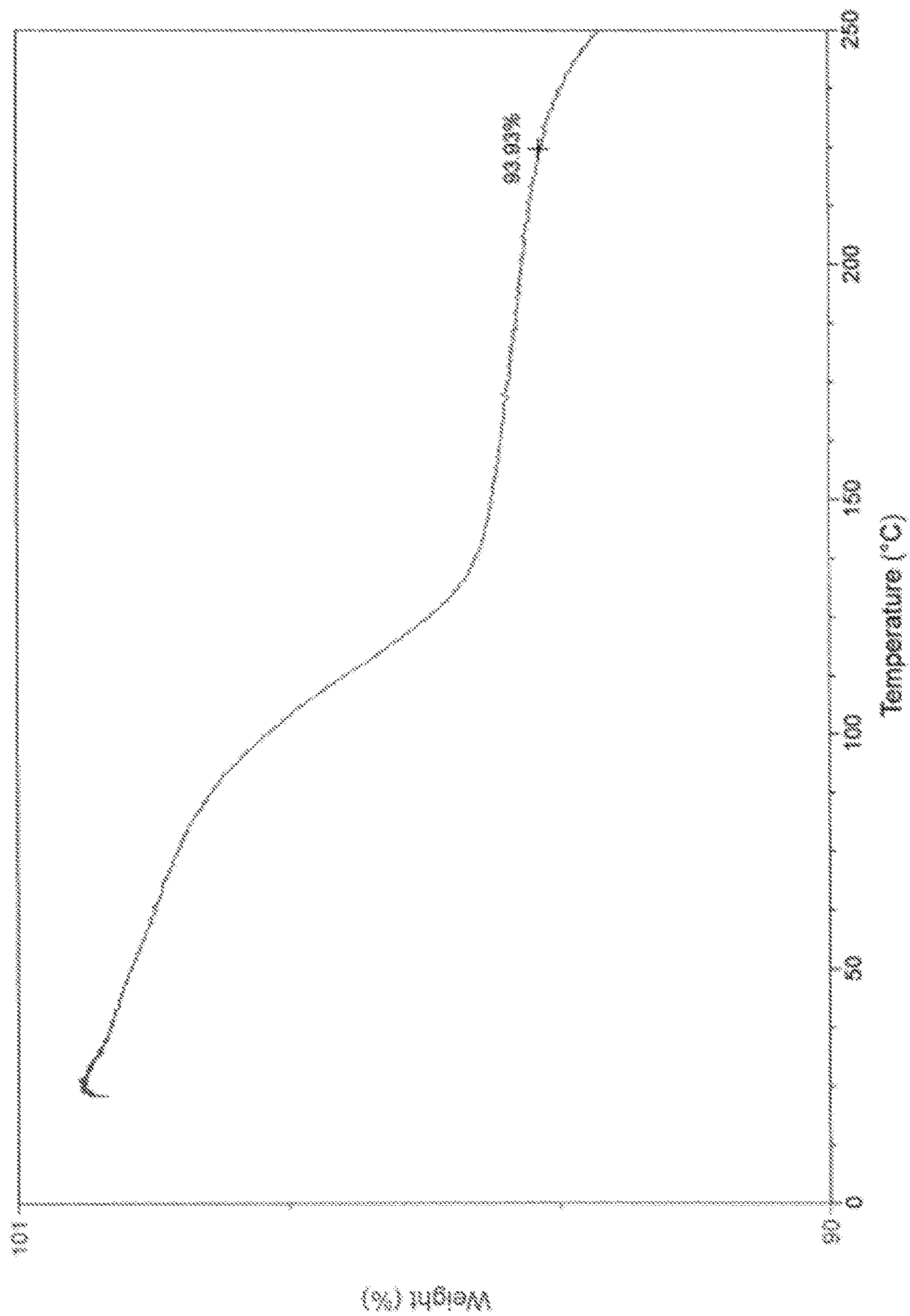
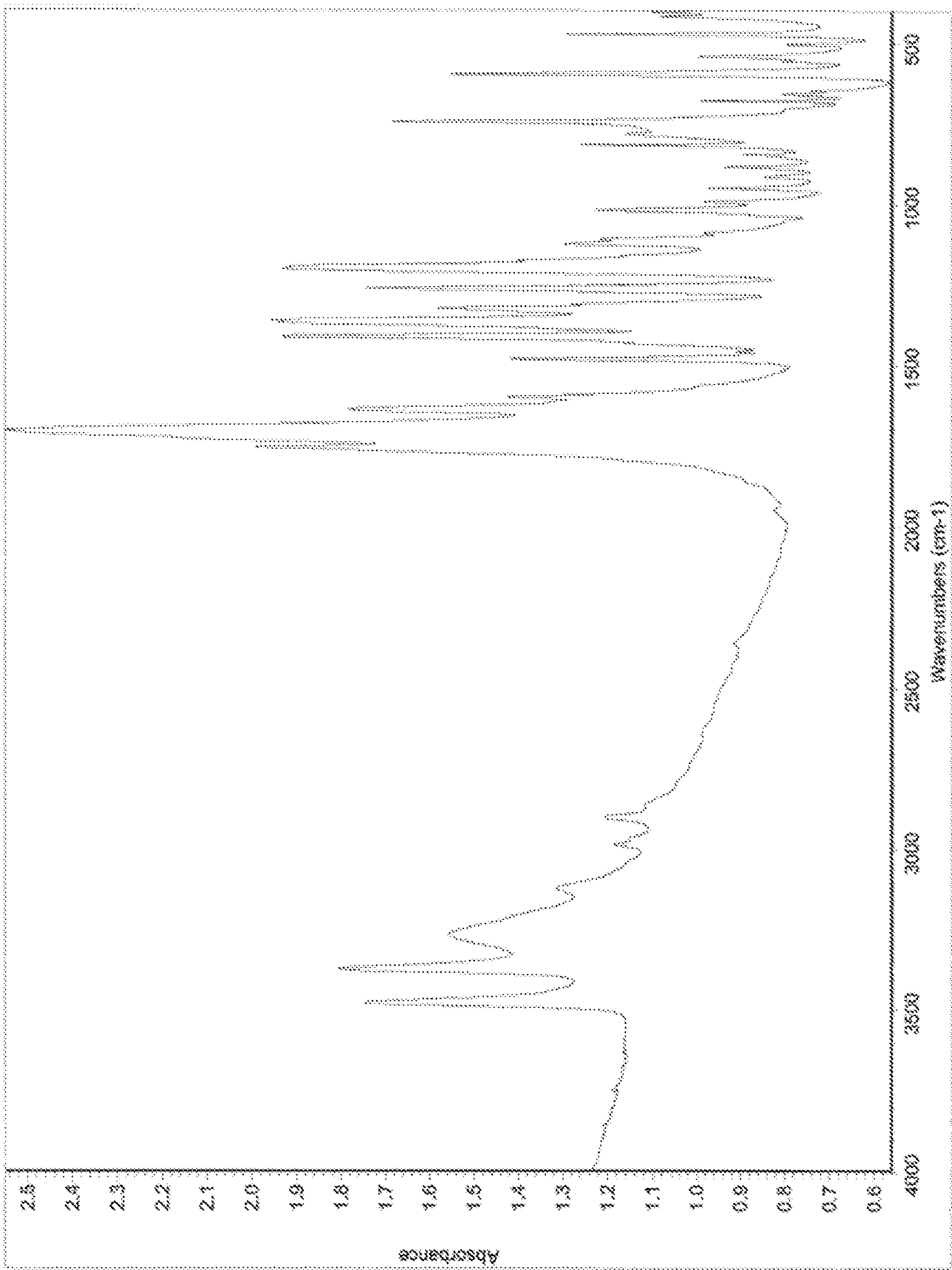


FIG. 4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CRYSTALLINE 4-AMINO-2-(2,6-DIOXOPIPERIDINE-3-YL) ISOINDOLINE-1,3-DIONE MONOHYDRATE, COMPOSITIONS AND METHODS OF USE THEREOF

This application is a continuation application of U.S. patent application Ser. No. 15/849,442, filed Dec. 20, 2017, which claims priority to U.S. Provisional Patent Application No. 62/562,280, filed Sep. 22, 2017, the entirety of each of which are incorporated herein by reference.

FIELD

Provided herein is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate. Pharmaceutical compositions comprising such solid and methods of use for treating, preventing, and managing various disorders are also provided herein.

BACKGROUND

Many compounds can exist in different crystal forms, or polymorphs, which exhibit different physical, chemical, and spectroscopic properties. For example, certain polymorphs of a compound may be more readily soluble in particular solvents, may flow more readily, or may compress more easily than others. See, e.g., P. DiMartino, et al., *J. Thermal Anal.,* 48:447-458 (1997). In the case of drugs, certain solid forms may be more bioavailable than others, while others may be more stable under certain manufacturing, storage, and biological conditions.

Polymorphic forms of a compound are known in the pharmaceutical arts to affect, for example, the solubility, stability, flowability, fractability, and compressibility of the compound, as well as the safety and efficacy of drug products comprising it. See, e.g., Knapman, K. *Modern Drug Discoveries,* 2000, 53. Therefore, the discovery of new polymorphs of a drug can provide a variety of advantages.

The identification and selection of a solid form of a pharmaceutical compound are complex, given that a change in solid form may affect a variety of physical and chemical properties, which may provide benefits or drawbacks in processing, formulation, stability, bioavailability, storage, handling (e.g., shipping), among other important pharmaceutical characteristics. Useful pharmaceutical solids include crystalline solids and amorphous solids, depending on the product and its mode of administration. Amorphous solids are characterized by a lack of long-range structural order, whereas crystalline solids are characterized by structural periodicity. The desired class of pharmaceutical solid depends upon the specific application; amorphous solids are sometimes selected on the basis of, e.g., an enhanced dissolution profile, while crystalline solids may be desirable for properties such as, e.g., physical or chemical stability.

Pomalidomide has a chemical name of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione. Pomalidomide is a compound that inhibits, for example, LPS induced monocyte TNFα, IL-1β, IL-12, IL-6, MIP-1, MCP-1, GM-CSF, G-CSF, and COX-2 production, and may be used in treating various disorders. See, e.g., U.S. Pat. Nos. 5,635,517, 6,316,471, 6,476,052, 7,393,863, 7,629,360, 7,863,297, 8,198,262, 8,673,939, 8,735,428, 8,759,375, 8,722,647, and 9,282,215. Pomalidomide has direct anti-myeloma tumoricidal and immunomodulatory activities, and inhibits stromal cell support for multiple myeloma tumor cell growth. Pomalidomide inhibits proliferation and induces apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibits the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergizes with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhances T cell- and natural killer (NK) cell-mediated immunity, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. Pomalidomide also inhibits angiogenesis by blocking the migration and adhesion of endothelial cells. A molecular target of pomalidomide is cereblon, a protein that forms a ubiquitin E3 ligase complex with DNA damage-binding protein (DDBA), culin 4 (CUL4) and protein Roc1. Pomalidomide binding to cereblon induces the polyubiquitination of two substrate proteins Ikaros (IKF1) and Aiolos (IKZF3). Pomalidomide is known to have CNS penetration. Due to its diversified pharmacological properties, pomalidomide is useful in treating, preventing, and/or managing various diseases or disorders.

Pomalidomide and methods of synthesizing pomalidomide are described, e.g., in U.S. Pat. Nos. 5,635,517, 6,335,349, 6,316,471, 6,476,052, 7,041,680, 7,709,502, and 7,994,327. The chemical structure of pomalidomide has been known since at least the 1960s, but little is known regarding solid forms. An amorphous solid and one crystalline form (anhydrous) have been described in WO 2013/126326. A novel crystalline form of pomalidomide is described herein.

Pomalidomide is the active ingredient in POMALYST®, which in combination with dexamethasone was approved by the FDA in 2013 for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated a disease progression on or within 60 days of completion of the last therapy. The label for POMALYST® can be found at http://www.pomalyst.com/?pi=yes&gclid=CMP4keDY-tMCFZOCfgods7oPsA.

New polymorphic forms of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione can further the development of formulations for the treatment of chronic illnesses, and may yield numerous formulation, manufacturing and therapeutic benefits.

SUMMARY

Provided herein is a crystalline form of pomalidomide. Also provided herein are pharmaceutical compositions comprising a crystalline form of pomalidomide. Further provided herein are methods of treating or preventing a variety of disease and disorders, which comprise administering to a patient a therapeutically effective amount of a crystalline form of pomalidomide. Also provided herein are methods of treating multiple myeloma, optionally in combination with dexamethasone.

Also provided herein are methods of preparing, isolating, and characterizing crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate provided herein.

Also provided herein are pharmaceutical compositions containing crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl) isoindoline-1,3-dione monohydrate provided herein.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** provides a representative X-ray powder diffraction (XRPD) pattern of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate.

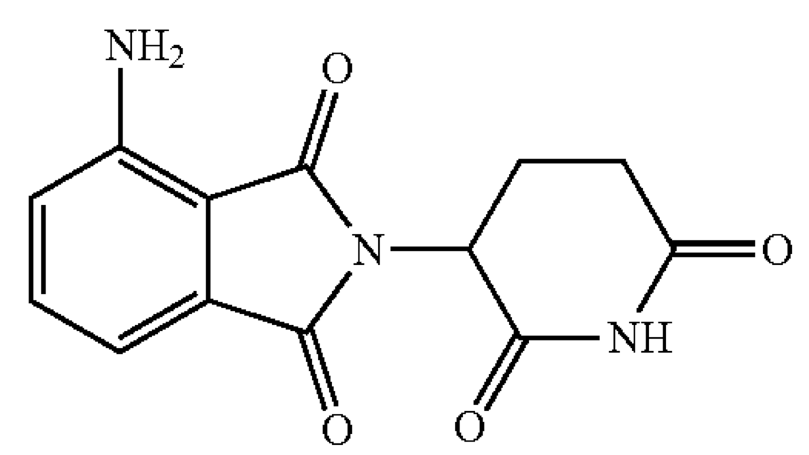
FIG. 2 provides a representative differential scanning calorimetry (DSC) thermogram of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate.

FIG. 3 provides a representative thermogravimetric analysis thermogram (TGA) of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate.

FIG. 4 provides a representative infrared (IR) spectrum of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate.

DEFINITIONS

As used herein, and unless otherwise specified, the compound referred to herein by the name pomalidomide or 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione, corresponds to a compound of Formula (I), depicted below.



(I)

Pomalidomide can be obtained via standard, synthetic methods (see, e.g., U.S. Pat. No. 5,635,517).

Unless otherwise specified, the term "crystalline" and related terms used herein, when used to describe a substance, component, product, or form, mean that the substance, component, product, or form is substantially crystalline, for example, as determined by X-ray diffraction. (see, e.g., *Remington's Pharmaceutical Sciences*, 20th ed., Lippincott Williams & Wilkins, Philadelphia Pa., 173 (2000); *The United States Pharmacopeia*, 37th ed., 503-509 (2014)).

As used herein, and unless otherwise specified, the terms "about" and "approximately," when used in connection with doses, amounts, or weight percents of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent that is recognized by one of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent. In certain embodiments, the terms "about" and "approximately," when used in this context, contemplate a dose, amount, or weight percent within 30%, within 20%, within 15%, within 10%, or within 5%, of the specified dose, amount, or weight percent.

As used herein, and unless otherwise specified, the terms "about" and "approximately," when used in connection with a numeric value or range of values which is provided to characterize a particular solid form, e.g., a specific temperature or temperature range, such as, for example, that describes a melting, dehydration, desolvation, or glass transition temperature; a mass change, such as, for example, a mass change as a function of temperature or humidity; a solvent or water content, in terms of, for example, mass or a percentage; or a peak position, such as, for example, in analysis by, for example, IR or Raman spectroscopy or XRPD; indicate that the value or range of values may deviate to an extent deemed reasonable to one of ordinary skill in the art while still describing the solid form. Techniques for characterizing crystal forms and amorphous forms include, but are not limited to, thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), single-crystal X-ray diffractometry, vibrational spectroscopy, e.g., infrared (IR) and Raman spectroscopy, solid-state and solution nuclear magnetic resonance (NMR) spectroscopy, optical microscopy, hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography and quantitative analysis, particle size analysis (PSA), surface area analysis, solubility studies, and dissolution studies. In certain embodiments, the terms "about" and "approximately," when used in this context, indicate that the numeric value or range of values may vary within 30%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1.5%, 1%, 0.5%, or 0.25% of the recited value or range of values. In the context of molar ratios, "about" and "approximately" indicate that the numeric value or range of values may vary within 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1.5%, 1%, 0.5%, or 0.25% of the recited value or range of values. It should be understood that the numerical values of the peaks of an X-ray powder diffraction pattern may vary from one machine to another, or from one sample to another, and so the values quoted are not to be construed as absolute, but with an allowable variability, such as ±0.2 degrees two theta (°2θ), or more. For example, in some embodiments, the value of an XRPD peak position may vary by up to ±0.2 degrees 2θ while still describing the particular XRPD peak.

As used herein, and unless otherwise specified, a solid form that is "substantially physically pure" is substantially free from other solid forms. In certain embodiments, a crystal form that is substantially physically pure contains less than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.05%, or 0.01% of one or more other solid forms on a weight basis. The detection of other solid forms can be accomplished by any method apparent to a person of ordinary skill in the art, including, but not limited to, diffraction analysis, thermal analysis, elemental combustion analysis and/or spectroscopic analysis.

As used herein, and unless otherwise specified, a solid form that is "substantially chemically pure" is substantially free from other chemical compounds (i.e., chemical impurities). In certain embodiments, a solid form that is substantially chemically pure contains less than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.05%, or 0.01% of one or more other chemical compounds on a weight basis. The detection of other chemical compounds can be accomplished by any method apparent to a person of ordinary skill in the art, including, but not limited to, methods of chemical analysis, such as, e.g., mass spectrometry analysis, spectroscopic analysis, thermal analysis, elemental combustion analysis and/or chromatographic analysis.

As used herein, and unless otherwise indicated, a chemical compound, solid form, or composition that is "substantially free" of another chemical compound, solid form, or composition means that the compound, solid form, or composition contains, in certain embodiments, less than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2% 0.1%, 0.05%, or 0.01% by weight of the other compound, solid form, or composition.

Unless otherwise specified, the terms "solvate" and "solvated," as used herein, refer to a solid form of a substance which contains solvent. The terms "hydrate" and "hydrated" refer to a solvate wherein the solvent is water. The term "monohydrate" refers to a hydrate containing approximately one mole of water per mole of compound.

As used herein, and unless otherwise specified, the terms "treat," "treating" and "treatment" refer to the eradication or amelioration of a disease or disorder, or of one or more symptoms associated with the disease or disorder. In certain embodiments, the terms refer to minimizing the spread or worsening of the disease or disorder resulting from the administration of one or more prophylactic or therapeutic agents to a subject with such a disease or disorder. In some embodiments, the terms refer to the administration of a compound provided herein, with or without other additional active agent, after the onset of symptoms of a particular disease.

Unless otherwise specified, the term "composition" as used herein is intended to encompass a product comprising the specified ingredient(s) (and in the specified amount(s), if indicated), as well as any product which results, directly or indirectly, from combination of the specified ingredient(s) in the specified amount(s). By "pharmaceutically acceptable," it is meant a diluent, excipient, or carrier in a formulation must be compatible with the other ingredient(s) of the formulation and not deleterious to the recipient thereof.

Unless otherwise specified, the term "subject" is defined herein to include animals, such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, and the like. In specific embodiments, the subject is a human.

Unless otherwise specified, to the extent that there is a discrepancy between a depicted chemical structure of a compound provided herein and a chemical name of a compound provided herein, the chemical structure shall control.

DETAILED DESCRIPTION

Crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate can be prepared by the methods described herein, including the methods described in the Example below, or by techniques known in the art, including heating, cooling, freeze drying, lyophilization, quench cooling the melt, rapid solvent evaporation, slow solvent evaporation, solvent recrystallization, antisolvent addition, slurry recrystallization, crystallization from the melt, desolvation, recrystallization in confined spaces such as, e.g., in nanopores or capillaries, recrystallization on surfaces or templates such as, e.g., on polymers, recrystallization in the presence of additives, such as, e.g., co-crystal counter-molecules, desolvation, dehydration, rapid cooling, slow cooling, exposure to solvent and/or water, drying, including, e.g., vacuum drying, vapor diffusion, sublimation, grinding (including, e.g., cryo-grinding, solvent-drop grinding or liquid assisted grinding), microwave-induced precipitation, sonication-induced precipitation, laser-induced precipitation and precipitation from a supercritical fluid. The particle size of the resulting solid forms, which can vary, e.g., from nanometer dimensions to millimeter dimensions, can be controlled, e.g., by varying crystallization conditions, such as, e.g., the rate of crystallization and/or the crystallization solvent system, or by particle-size reduction techniques, e.g., grinding, milling, micronizing or sonication.

While not intending to be bound by any particular theory, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate is characterized by physical properties, e.g., stability, solubility and dissolution rate, appropriate for pharmaceutical and therapeutic dosage forms. Moreover, while not wishing to be bound by any particular theory, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate is characterized by physical properties (e.g., density, compressibility, hardness, morphology, cleavage, stickiness, solubility, water uptake, electrical properties, thermal behavior, solid-state reactivity, physical stability, and chemical stability) affecting particular processes (e.g., yield, filtration, washing, drying, milling, mixing, tableting, flowability, dissolution, formulation, and lyophilization) which make certain solid forms suitable for the manufacture of a solid dosage form. Such properties can be determined using particular analytical chemical techniques, including solid-state analytical techniques (e.g., X-ray diffraction, microscopy, spectroscopy and thermal analysis), as described herein and known in the art.

Certain embodiments herein provide compositions comprising crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl) isoindoline-1,3-dione monohydrate. Certain embodiments provide compositions of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate in combination with other active ingredients. Certain embodiments provide methods of using these compositions in the treatment, prevention or management of diseases and disorders including, but not limited to, the diseases and disorders provided herein.

Certain embodiments herein provide crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrates can be obtained from a 2:1 THF/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrates can be obtained from a 1:12 1,2-dioxane/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrates can be obtained from a 1:1 1,4-dioxane/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrates can be obtained from a 1:1:1 acetone/isopropanol alcohol/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrates can be obtained from a 2:1:1 ethanol/THF/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrates can be obtained from a 1:1 1,4-dioxane/water mixture. In one embodiment provided herein, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrates can be obtained from a 1:1 ethanol/water mixture.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate.

In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate may be characterized by X-ray powder diffraction analysis.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having an X-ray powder diffraction pattern comprising peaks at 11.8, 17.1, and 24.2 degrees 2θ±0.2 degrees 2θ.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate wherein the X-ray powder diffraction pattern further comprises peaks at 13.9, 16.5, and 25.7 degrees 2θ±0.2 degrees 2θ.

In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate is characterized by XRPD peaks located at one, two, three, four, five, six, seven, eight, nine, ten, eleven or twelve of the following approximate positions: 8.3, 11.3, 11.8, 12.7, 13.9, 16.1, 16.5, 17.1, 18.3, 19.1, 19.6, 23.8, 24.2, 24.7, 25.7, 26.9, 27.2, 27.9, 28.5, 29.5, 32.1, 32.6, and 33.9 degrees 2θ. In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate is characterized by an XRPD pattern which matches the pattern exhibited in FIG. **1**. In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate is characterized by an XRPD pattern having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 peaks matching peaks in the representative XRPD pattern provided herein.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having an X-ray powder diffraction pattern corresponding to the representative X-ray powder diffraction patterns depicted in FIG. **1**.

In certain embodiments, crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate may be characterized by thermal analysis.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a differential scanning calorimetry thermogram comprising an endotherm with a maximum at about 312° C.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a differential scanning calorimetry thermogram corresponding to the representative differential scanning calorimetry thermograms depicted in FIG. **2**.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having approximately 6.2% of water by mass.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 6.1% when heated from about 30° C. to about 225° C.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 4.9% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 5.6% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 5.7% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 5.8% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 6.1% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 6.5% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 6.7% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 6.8% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 6.9% when heated from about 30° C. to about 225° C. In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of about 7.4% when heated from about 30° C. to about 225° C.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram comprising a weight loss of between about 4.9% and about 7.4% when heated from about 30° C. to about 225° C.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having a thermogravimetric analysis thermogram corresponding to the representative thermogravimetric analysis thermogram depicted in FIG. **3**.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate having an infrared spectrum corresponding to the representative infrared spectrum depicted in FIG. **4**.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate which is substantially physically pure.

In one embodiment, provided is a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate which is substantially chemically pure.

In one embodiment, provided is a pharmaceutical composition comprising a crystal form of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate.

Pharmaceutical Compositions

Pharmaceutical compositions and single unit dosage forms comprising crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate are provided herein. Also provided herein are methods for preparing pharmaceutical compositions and single unit dosage forms comprising crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate. For example, in certain embodiments, individual dosage forms comprising crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate provided herein or prepared using crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate provided herein may be suitable for oral, mucosal (including rectal, nasal, or vaginal), parenteral (including subcutaneous, intramuscular, bolus injection, intraarterial, or intravenous), sublingual, transdermal, buccal, or topical administration.

In certain embodiments, pharmaceutical compositions and dosage forms provided herein comprise crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate. Certain embodiments herein provide pharmaceutical compositions and dosage forms comprising a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate, wherein the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate is substantially pure. Certain embodiments herein provide pharmaceutical compositions and dosage forms comprising a crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate as provided herein, which is substantially free of other crystalline solid forms of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione and/or amorphous solid forms of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione. Pharmaceutical compositions and dosage forms provided herein typically also comprise one or more pharmaceutically acceptable excipients, diluents or carriers.

Single unit dosage forms provided herein are suitable for oral or parenteral (e.g., subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial) administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules powders and sterile solids that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

Capsules may contain a shell.

The composition, shape, and type of dosage forms provided herein will typically vary depending on their use. A parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease or disorder. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. See, e.g., *Remington's Pharmaceutical Sciences,* 18th ed., Mack Publishing, Easton Pa. (1990).

Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form.

In one embodiment, suitable excipients include mannitol, pregelatinized starch, and sodium stearyl fumarate.

Capsule shells may contain gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, white ink, and black ink.

Capsule shells may contain gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, FD&C red 3, and white ink.

Capsule shells may contain gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, and white ink.

Capsule shells may contain gelatin, titanium dioxide, FD&C blue 1, FD&C blue 2, and white ink.

Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms provided herein lie within the range of from about 0.1 mg to about 1,000 mg per day, given as a single once-a-day dose in the morning or as divided doses throughout the day. More specifically, the daily dose may be administered twice, three times, or four times daily in equally divided doses. Specifically, a daily dose range may be from about 0.1 mg to about 500 mg per day, more specifically, between about 0.1 mg and about 200 mg per day. A daily dose range may be 1 mg, 2 mg, 3 mg, 4 mg, or 5 mg. In managing the patient, the therapy may be initiated at a lower dose, perhaps about 1 mg to about 25 mg, and increased if necessary up to about 200 mg to about 1,000 mg per day as either a single dose or divided doses, depending on the patient's global response.

Oral Dosage Forms

Pharmaceutical compositions provided herein that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally *Remington's Pharmaceutical Sciences,* 18th ed., Mack Publishing, Easton Pa. (1990).

Typical oral dosage forms provided herein are prepared by combining the active ingredient(s) in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101™,

AVICEL-PH-103™, AVICEL RC-581™, AVICEL-PH-105™ (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, Pa.), and mixtures thereof. A specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-58™. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM™.

Disintegrants are used in the compositions provided herein to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, specifically from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms provided herein include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

Lubricants that can be used in pharmaceutical compositions and dosage forms provided herein include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200™, manufactured by W.R. Grace Co. of Baltimore, Md.), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, Tex.), CAB-O-SIL™ (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass.), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about one weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

Parenteral Dosage Forms

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial injection. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms provided herein are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms provided herein.

EXAMPLES

Preparation of crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate: 10 mg of pomalidomide Form A (anhydrate) was placed in a 50 mL round bottom flask with 20 mL THF and 10 mL water. The flask was then placed on a rotary evaporator with the bath temperature at 80° C. All of the pomalidomide dissolved. An aspirator vacuum was then applied and the yellow crystalline solid was obtained within about two minutes. The solid was further air dried by exposure to the laboratory atmosphere for 25 days.

Karl-Fischer titration revealed the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate contained 6.3% water.

XRPD data for the crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate is shown below in Table 1.

Scan Type: Normal
Start Angle: 3 deg
Stop Angle: 35 deg.
Num Points: 1601
Step Size: 0.02 deg.
Datafile Res: 1600
Scan Rate: 0.001000
Scan Mode: Step
Wavelength: 1.540562 Å

Tube divergent	2.00 mm
Tube scatter	4.00 mm
Detector scatter	0.50 mm
Detector reflection	0.30 mm

TABLE 1

XRPD data for crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate.

Peaks: (Deg.)	Position (Dsp.)	Intensity (cps)	Rel. Int. %
8.3	10.6504	123.31	17.67
11.3	7.7913	163.28	23.39
11.8	7.4995	559.60	80.17
12.7	6.9455	105.26	15.08
13.9	6.3726	340.48	48.78
16.1	5.5041	103.76	14.87
16.5	5.3709	259.85	37.23
17.1	5.1943	697.98	100.00
18.3	4.8425	226.92	32.51
19.1	4.6392	92.73	13.29
19.6	4.5161	87.72	12.57
23.8	3.7408	192.38	27.56
24.2	3.6695	483.43	69.26
24.7	3.5969	207.62	29.75
25.7	3.4685	338.07	48.43
26.9	3.3145	126.32	18.10
27.2	3.2752	100.75	14.43

TABLE 1-continued

XRPD data for crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate.

Peaks: (Deg.)	Position (Dsp.)	Intensity (cps)	Rel. Int. %
27.9	3.1956	152.38	21.83
28.5	3.1315	220.72	31.62
29.5	3.0280	134.34	19.25
32.1	2.7884	130.83	18.74
32.6	2.7472	95.74	13.72
33.9	2.6410	123.31	17.67

Additional experiments to prepare crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate are listed below.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:12 1,4-dioxane:water solution at 60° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator, triturated with water, and vacuum dried at rt for 2 hours. The resulting solid was found to have 6.1% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 2:1 THF:water solution at 80° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator and air dried. The resulting solid was found to have 5.8% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1 1,4-dioxane:water solution at 85° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator and air dried overnight. The resulting solid was found to have 6.7% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1 1,4-dioxane:water solution at 80° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator, triturated with water. The resulting solid was found to have 6.5% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1 1,4-dioxane:water solution at 90° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator, triturated with water, vacuum dried, 100 C for 1 h. The resulting solid was found to have 5.8% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1:1, acetone:IPA:water solution at 90° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator, dried overnight at rt, vacuum for 0.5 h. The resulting solid was found to have 4.9% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 2:1:1 ethanol:THF:water solution at 95° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator. The resulting solid was found to have 5.7% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1 1,4-dioxane:water solution at 80° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator, triturated with water, and dried under vacuum. The resulting solid was found to have 5.6% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1 ethanol:water solution at 80° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator. The resulting solid was found to have 7.4% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1 ethanol:water solution at 80° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator. The resulting solid was found to have 6.9% water by TGA analysis.

ca. 50 mg pomalidomide Form A (anhydrate) was dissolved in a 1:1 ethanol:water solution at 80° C. The pomalidomide dissolved completely in the solution. The solution was taken to dryness on a rotary evaporator, and further dried at 50° C. for 2 h. The resulting solid was found to have 6.8% water by TGA analysis.

Additional Experiments that Did not Result in crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate

The following unsuccessful experiments were performed by mixing in a flask Form A of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione with solvents until dissolution, then the flask was placed on a rotoevaporator (fast rotation; vacuum by water aspirator) at various bath temperatures until dryness or until apparent dryness.

Certain experiments produced an oil, which were then triturated as follows: pure HPLC grade water was added to flask containing the oil, and the flask was stirred. If a solid was formed, it was further dried.

TABLE 2

Conditions that did not result in a crystalline monohydrate of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione.

Solvent	Co-solvent	Ratio of solvent/co-solvent	Temperature (° C.)	Notes
1,4-dioxane	N/A		60	
THF	Water	10:1	60	Triturated vacuum dried
THF	Water	1:1	80	
Ethanol	Water	1:1	80	100° C. for 12 hours after initial drying
Ethanol	Water	1:1	80	Dried further for 20 min at 100° C., then 30 min at 150° C.
THF	Water	1:1	80	
1,4-dioxane	Water	1:1	80	
THF	Water	24:5	80	

TABLE 2-continued

Conditions that did not result in a crystalline monohydrate of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione.

Solvent	Co-solvent	Ratio of solvent/co-solvent	Temperature (° C.)	Notes
THF	Water	23:5	80	
1,4-dioxane	Water	1:1	80	Triturated, dried at 150° C. for 1 h
THF	Water	95:5	65	
Ethanol	Water	95:5	90	
Ethanol	Water	98:2	90	
THF	Water	9:1	85	
Ethanol	THF/Water	2:1:2	60	
Ethanol	THF/Water	2:1:2	95	
Ethanol	THF/Water	1:6:1	95	
Ethanol	THF/Water	6:4:1	95	
Ethanol	THF/Water	1:2:1	95	
1,4-dioxane	Water	1:1	95	Triturated
1,4-dioxane	Water	1:1	95	Triturated, air tried, 45 m in vacuo
Ethanol	THF/Water	3:5:3	80	Air dried 3 h
Ethanol	THF/Water	3:5:3	80	
Acetone	i-PrOH/Water	1:1:1	90	
Acetone	i-PrOH/Water	1:1:1	95	Material was moist
Acetone	i-PrOH/Water	1:1:1	95	Air dried 18 h
Acetone	i-PrOH/Water	1:1:1	95	Air current dried 3 h
Acetone	i-PrOH/Water	1:1:1	95	Air current dried 1 h
Acetone	i-PrOH/Water	1:1:1	85	
1,4-dioxane	Water	1:1	85	Material was moist
THF	Water	1:1	80	Air dried
THF	Water	1:1	80	Dried in vacuo for 2 h at 200° C.
1,4-dioxane	Water	1:1	90	Triturated, dried in vacuo 16 h
THF	Water	4:1	95	
THF	Water	4:1	80	
THF	Water	4:1	65	
1,4-dioxane	Water	1:1	95	
1,4-dioxane	Water	4:1	80	Oil, triturated, air dried 4 h
1,4-dioxane	Water	3:1	85	Air dried 3 h
1,4-dioxane	Water	3:1	85	Dried overnight at room temperature
1,4-dioxane	Water	3:1	85	Triturated, dried
THF	Water	4:1	80	Air dried 1 h
THF	Water	12:1	70	Air dried
THF	Water	6:1	80	Air dried
MeCN	Water	2:1	80	Material was moist
MeCN	Water	2:1	80	Dried overnight
MeCN	Water	2:1	90	Air dried
1,4-dioxane	Ethanol/THF/Water	1:1:1:2	85	Air dried
1,4-dioxane	THF/Water	6:6:1	50	Material was moist
1,4-dioxane	THF/Water	6:6:1	50	Dried at 90° C. in vacuo
1,4-dioxane	THF/Water	6:6:1	50	Air dried
Acetone	THF/Water	10:3:3	90	Air dried
THF	Water	25:1	60	Air dried
THF	Water	25:1	60	
THF	Water	20:1	70	
THF	Water	4:1	80	Air dry
THF	Water	10:1	65	Air dry
THF	Water	10:1	75	
Acetone	THF/Water	10:1:1	60	Air dry
1,4-dioxane	Water	3:1	85	Triturated
1,4-dioxane	Water	12:1	60	Triturated

Characterization Methodology

Samples generated as described in the solid form screen were typically analyzed by X-Ray Powder Diffraction (XRPD). XRPD was conducted on a Scintag X2 X-ray powder diffractometer using Cu Kα radiation at 1.54 Å. In general, positions of XRPD peaks are expected to individually vary on a measurement-by-measurement basis by about ±0.2° 2θ. In general, as understood in the art, two XRPD patterns match one another if the characteristic peaks of the first pattern are located at approximately the same positions as the characteristic peaks of the second pattern. As understood in the art, determining whether two XRPD patterns match or whether individual peaks in two XRPD patterns match may require consideration of individual variables and parameters such as, but not limited to, preferred orientation, phase impurities, degree of crystallinity, particle size, variation in diffractometer instrument setup, variation in XRPD data collection parameters, and/or variation in XRPD data processing, among others. The determination of whether two patterns match may be performed by eye and/or by computer analysis. An example of an XRPD pattern collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. **1**.

Differential Scanning Calorimetry (DSC) analyses were performed on a TA Instruments Q100™. About 5 mg of sample was placed into a tared DSC closed aluminum pan and the weight of the sample was accurately recorded. An example of a DSC thermogram collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. **2**.

Thermal Gravimetric Analyses (TGA) were performed on a TA Instruments Q50™ About 10 mg of sample was placed on an open aluminium pan, accurately weighed and loaded into the TGA furnace.

An example of a TGA thermogram collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. **3**.

Water determination by the Karl Fischer method was performed using a Metrohm 831 KF Coulometer. The sample was dissolved in anhydrous acetone and injected into the titrator.

Infrared spectroscopy was performed using a ThermoNicolet Nexus 670 spectormeter. A sample of ca. 1 mg of the monohydrate in ca. 100 mg KBr. The mixture was then pressed into a pellet, which was used for the IR study. An example of an IR spectrum collected and analyzed using these methods and parameters is provided herein, e.g., as FIG. **4**.

The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the disclosure and are encompassed by the appended claims.

Citation or identification of any reference in this application is not an admission that such reference is available as prior art. The full scope of the disclosure is better understood with reference to the appended claims.

The invention claimed is:

1. Crystalline 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione monohydrate, having an X-ray powder diffraction pattern comprising peaks at 11.8, 17.1, and 24.2 degrees 2θ±0.2 degrees 2θ, which is substantially physically pure.

2. The monohydrate of claim **1**, wherein the X-ray powder diffraction pattern further comprises peaks at 13.9, 16.5, and 25.7 degrees 2θ±0.2 degrees 2θ.

3. The monohydrate of claim **1**, having an X-ray powder diffraction pattern corresponding to the representative X-ray powder diffraction pattern depicted in FIG. **1**.

4. The monohydrate of claim **1**, having a differential scanning calorimetry thermogram comprising an endotherm with a maximum at about 312° C.

5. The monohydrate of claim **1**, having a differential scanning calorimetry thermogram corresponding to the representative differential scanning calorimetry thermogram depicted in FIG. **2**.

6. The monohydrate of claim **1**, having about 6.2% of water by mass.

7. The monohydrate of claim **1**, having a thermogravimetric analysis thermogram comprising a weight loss of between about 4.9% and about 7.4% when heated from about 30° C. to about 225° C.

8. The monohydrate of claim **1**, having a thermogravimetric analysis thermogram corresponding to the representative thermogravimetric analysis thermogram depicted in FIG. **3**.

9. The monohydrate of claim **1**, having an infrared spectrum corresponding to the representative infrared spectrum depicted in FIG. **4**.

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